WHEN SHOULD CLINICIANS WORRY ABOUT BONE DENSITY FOR PATIENTS WITH EPILEPSY?

Progressive Bone Deficit in Epilepsy. Sheth RD, Binkley N, Hermann BP. *Neurology* 2008;70(3):170–176. OBJECTIVE: Chronic treatment with antiepileptic medication is associated with reduced bone mineral density (BMD), which may underlie the two- to sixfold increase in fracture rates observed in patients with epilepsy. The objective was to determine the timing of the BMD deficit in ambulatory children with epilepsy. METHODS**:** A cross-sectional evaluation was conducted in 82 ambulatory children aged 6 to 18 years (12.4 ± 3.3 years) with epilepsy for <1 year (n = 18), 1 to 5 years (n = 37), and 6 or more years (n = 27). Controls were 32 healthy children aged 12.8 ± 2.6 years. Age- and sex-corrected total body BMD Z-score was measured. RESULTS**:** Total BMD Z-score was lower in children with epilepsy (0.10 ± 0.96; CI = −0.08, 0.34) compared to controls (0.57 ± 0.74; CI = 0.3, 0.84; $p = 0.03$). Increasing duration of epilepsy was associated with a progressive reduction in BMD compared to controls (Spearman $r = -0.197$; $p = 0.03$). Compared to controls, those with epilepsy for 1 to 5 years had a mean BMD Z-score of 0.13 ± 0.78 (CI = −0.13, 0.39; $p = 0.04$) and in those treated for 6 or more years BMD was 0.06 ± 1.11 (CI = −0.38, 0.5; $p = 0.04$). For those with epilepsy for <1 year BMD was 0.23 ± 1.1 (CI = −0.31, 0.77; $p = 0.21$). CONCLUSIONS: Children treated for epilepsy sustain significant bone mineral density (BMD) deficit compared to controls during the initial 1 to 5 years of treatment which progressively worsens thereafter. This progressive BMD deficit may be a contributing factor to the increased fracture risk observed in patients with epilepsy and may accelerate aging-related osteoporosis.

COMMENTARY

Epilepsy is associated with an increased risk of fractures. These fractures can be a direct result of injury sustained during a seizure or falls due to impaired coordination from antiepileptic drugs. However, individuals with epilepsy also have an increased risk of unexpected pathological fractures that occur during normal activity (1) and an increased incidence of osteopenia or osteoporosis that predispose them to pathologic as well as traumatic fractures (2). There is evidence that chronic treatment with enzyme-inducing antiepileptic drugs may reduce bone density through increased metabolism of vitamin D; however, at least one nonenzyme inducing antiepileptic drug, valproate, also may reduce bone density (3). It is clear that drug-induced reduction in bone density may have several mechanisms (4). One study suggested that reduction in bone mineral density may be observed within 1 year of treatment with phenytoin (5), but the temporal pattern of reduced bone density generally is not known.

In their cross-sectional study of bone mineral density among children with epilepsy, Sheth and colleagues found only a trend toward reduced bone mineral density in children treated for less than 1 year, but a statistically significant reduction was seen after 1 year of treatment. The group of children treated for 6 or more years had the greatest reduction in bone mineral density and included two girls who had experienced pathological fractures. The authors investigated possible other contributing factors in reduced bone density. For instance, they calculated calcium intake, using a 3-day questionnaire, and found no effect on bone density. Similarly, growth metrics did not distinguish patients from controls. Based on activity logs, physical activity also was not different between the controls and children who had had epilepsy for less than 6 years but was reduced in children with epilepsy ≥6 years.

The study of Sheth and colleagues was not designed to assess the effect of specific antiepileptic medications on bone density, because the patients with the greatest reduction in bone density often were treated with more than one antiepileptic drug. Earlier studies implicated several of the old antiepileptic drugs in bone density reduction, but only limited information is available for the new antiepileptic drugs, which theoretically are expected to have less effect on bone density because they are less likely to induce liver enzymes. However, while preliminary data are favorable for lamotrigine (5,6), they do not suggest an advantage for oxcarbazepine over carbamazepine (7,8). Importantly, all of this emphasizes the need for studies to identify antiepileptic drugs that are not associated with reduction in bone density.

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Sheth et al. point out that puberty and adolescence are periods of rapid growth and bone mineral density accrual, emphasizing that reduction in bone mineral density during this period of life could be particularly deleterious to bone health. Their hypothesis could be investigated by measuring bone density in patients with seizure onset before puberty and then comparing it with patients who have seizure onset after puberty. A recent study involving ambulatory patients with epilepsy showed greater reduction in bone density in adults than in children as well as different independent predictors of bone mineral density reduction between children and adults: polytherapy in the pediatric group and both duration of treatment and use of enzyme-inducing drugs in the adult group were the key factors (9).

As a result of the findings of Sheth and colleagues, patients with epilepsy treated for 1 year or longer should be considered for bone density assessment. Prophylactic supplementation with calcium and vitamin D is often recommended for individuals considered at risk of reduced bone density from antiepileptic drugs, without data to indicate that this supplementation will prevent osteopenia. One study demonstrated that vitamin D supplementation increased bone density after 1 year of treatment for ambulatory patients taking antiepileptic drugs (10). Children derived equal benefit from 400 IU and 2,000 IU per day, while adults only benefited from high-dose vitamin D (4,000 IU per day). Although calcium supplementation also is recommended, the recommendation is not evidence-based for individuals with epilepsy. A large multicenter study is urgently needed to guide the clinician in the prevention and treatment of osteopenia for patients with epilepsy.

by Bassel W. Abou-Khalil, MD

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Is Seizure Surgery an Option for Patients with Very Low IQ?

Seizure Outcome after Resective Epilepsy Surgery in Patients with Low IQ. Malmgren K, Olsson I, Engman E, Flink R, Rydenhag B. *Brain* 2008;131(Pt 2):535–542. Epilepsy surgery has been questioned for patients with low IQ, since a low cognitive level is taken to indicate a widespread disturbance of cerebral function with unsatisfactory prognosis following resective surgery. The prevalence of epilepsy in patients with cognitive dysfunction is, however, higher than in the general population and the epilepsy is often more severe and difficult to treat. It is therefore important to try to clarify whether IQ predicts seizure outcome after resective epilepsy surgery. The Swedish National Epilepsy Surgery Register, which includes data on all epilepsy surgery procedures in Sweden since 1990, was analysed for all resective procedures performed 1990–99. Sustained seizure freedom with or without aura at the 2-year follow-up was analysed as a function of pre-operative IQ level categorized as IQ <50, IQ 50–69 and IQ ≥70 and was also adjusted for the following variables: age at epilepsy onset, age at surgery, pre-operative seizure frequency, pre-operative neurological impairment, resection type and histopathological diagnosis. Four hundred and forty-eight patients underwent resective epilepsy surgery in Sweden from 1990 to 1999 and completed the 2-year follow-up: 72 (16%) had IQ <70, (18 with IQ <50 and 54 with IQ 50–69) and 376 IQ ≥70. There were 313 adults and 135 children ≤18 years. Three hundred and twenty-five patients underwent temporal lobe resections (TLR) and 123 underwent various extratemporal resections (XTLR). At the 2-year follow-up, 56% (252/448) of the patients were seizure free: 22% (4/18) in the IQ <50 group, 37% (20/54) in the IQ 50–69 group and 61% (228/376) in the IQ ≥70 group. There was a significant relation between IQ category and seizure freedom [odds ratio (OR) 0.41, 95% confidence interval (CI) 0.27–0.62] and this held also when adjusting for clinical variables [OR 0.58 (95% CI 0.35–0.95)]. In this population-based epilepsy surgery series, IQ level was shown to be an independent predictor of seizure freedom at the 2-year follow-up. However, many of the low-IQ patients benefit from surgery, especially patients with lesions. Low IQ should not exclude patients from resective epilepsy surgery, but is an important prognostic factor to consider in the counselling process.

COMMENTARY

Although epilepsy surgery frequently offers the best hope for seizure control in patients with medically intractable epilepsy, a subset of patients fails to benefit despite exhaustive presurgical testing. Clinicians involved in the presurgical evaluation have long sought to understand factors that might predict postoperative seizure control. To date, structural imaging has proven most useful for defining the chances of postoperative seizure control (1). Independent predictors would be helpful, however, especially when MRI provides an ambiguous prognosis, such as patients with temporal lobe epilepsy and a normal MRI, who have roughly a 50/50 chance of gaining complete seizure control (2).

IQ measurements assess a wide range of cognitive functions, and outcomes are most strongly altered by conditions that diffusely injure the brain. Patients with lower IQ might be expected to have diffuse seizure onset zones or multifocal epilepsy, making surgery less effective. Based on this concern, some programs limit surgery for patients with low IQ. Malmgren and colleagues utilize the Swedish National Epilepsy Surgery Register to retrospectively analyze the relationship between IQ and postoperative seizure control for patients in Sweden. Their finding that patients with lower IQ have a poor prognosis for complete seizure control supports the hypothesis that seizures may be less likely to arise from a discrete focus in patients with low IQ. However, the investigators found that patients with low IQ did not have higher risks for surgical complications.

Malmgren et al. acknowledge that prior studies on this topic have shown variable results (3–5). Yet, in these previous investigations, the number of patients with a very low IQ has been small and the results usually have not been subjected to multivariate analysis. Other studies have controlled for important factors, such as pathology or type of surgery, and the data suggest a modest association between low IQ and poor surgical outcomes (4,6). Malmgren and colleagues note that patients with a low IQ are underrepresented in epilepsy surgery series. Furthermore, reports from different countries vary considerably. Only 2 to 3 percent of patients in a large epilepsy surgery series from the United States had an IQ below 70 (4), while in contrast, 16% of patients in the present series had an IQ below 70 and 4% had an IQ below 50. The authors speculate that both referring physicians and epileptologists may be reluctant to recommend surgery to patients with low IQ for fear of poor outcomes. They also suggest that the most impaired patients may be cared for by physicians who are less attuned to surgical options. While the authors focus on reasons that physicians might under-refer patients with low IQ, they do not address patient or family preference as a factor. For example, some patients with rare but persistent seizures aggressively seek complete seizure freedom so that they can drive. In the absence of this social motivation, caregivers for patients with low IQ might not wish to risk surgery if their loved one is experiencing only

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occasional or mild seizures. Furthermore, patients making their own decisions about surgical risks may have a different threshold for pursuing surgery than caregivers who are making the decision on behalf of another person. The authors also allude to there being less reluctance in Sweden and Norway to offer epilepsy surgery to patients with severe intellectual impairment than in the United States. It would have been helpful if Malmgren and colleagues had elaborated on common practice in these countries to back their assertion. If the authors are correct in this regard, their series may be less prone to selection bias than those performed in countries for which only the rare patient with low IQ is accepted for surgery.

The study has various limitations that must be considered. The inclusion of both adults and children resulted in methods for IQ determination that were not the same for all patients. Additionally, historical coding options in the national register did not allow for pathology to be categorized in a way that would be clinically most useful; for instance, mesial temporal sclerosis was lumped with gliosis. Consequently, it is not completely clear how much predictive value an IQ score adds to current, best preoperative prognostic factors. Finally, surgery type was dichotomized to temporal versus extratemporal and fails to take into account the fact that multilobar resection was five times more common in the patients with an IQ less than 70. Indeed, one possible reason that some of the patients with low IQ had excellent surgical outcomes is that early diffuse brain injury with attendant cortical reorganization of critical functions away from the seizure focus allowed extensive surgery to be undertaken with less risk for the development of new cognitive deficits than in patients with normal IQ.

While it seems likely that IQ is a modest, independent predictor of surgical outcome, it is not entirely clear how it can contribute to counseling individuals for epilepsy surgery. Until further studies clarify the issue, it is probably safest to not be specific with numerical estimates of the probability of surgical success when counseling the guardians of patients with low IQ. While the implication for counseling is uncertain, the take home message from this series is clear: many patients with very low IQ will benefit from operative treatment, and IQ should not be used to exclude patients from surgery.

by Paul Garcia, MD

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A Frontal Assault on the Generalized Nature of Juvenile Myoclonic Epilepsy

Frontal Cognitive Dysfunction in Juvenile Myoclonic Epilepsy. Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. *Epilepsia* 2008;49(4):657–662. PURPOSE: The aim of the present study was to investigate the possible frontal cognitive dysfunction in patients with juvenile myoclonic epilepsy (JME) and to compare the results with those of patients with frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE), as well as with controls. METHODS: A total of 50 patients with JME, 40 patients with FLE, 40 patients with TLE, and 40 normal controls, all matched for age, education, and IQ, were administered tests to assess frontal functions (the Word Fluency Test and the Wisconsin Card Sorting Test [WCST]). All participants had a normal intelligence level based on the Wechsler Adult Intelligence Scale, and did not take medications other than antiepileptics (AEDs) or have a psychiatric history. RESULTS: Patients with JME had severe impairment in all administered tasks, similar to that of patients with FLE; TLE patients and controls followed in order. Multiple regression analysis did not disclose any significant effect of clinical variables on the cognitive deficits. DISCUSSION: These results clearly suggest that JME patients can show some frontal dysfunction, which may affect both epileptogenic features and cognitive processes. Further studies are needed to confirm these findings.

COMMENTARY

Juvenile myoclonic epilepsy (JME) is considered the prototype of an idiopathic generalized epilepsy because the seizures are generalized, EEG discharges have a generalized distribution over the entire head, neurological examination is normal, and there is no evidence of focal brain pathology on routine neuroimaging. Nevertheless, there is emerging anatomic, physiological, and now cognitive evidence of focal frontal lobe abnormalities in JME. These findings could have far reaching implications: if focal abnormalities exist in JME, then it is possible that they exist in other idiopathic generalized epilepsies, fundamentally changing current understanding of their pathophysiology.

It is presumed that the basic pathophysiology of seizures associated with idiopathic generalized epilepsies, including JME, involves thalamocortical interactions that set up a reverberatory circuit between specific thalamic nuclei and broad (i.e., "generalized") regions of cortex. However, there is some physiological evidence of preferential frontal lobe involvement with JME. In the simplest sense, generalized discharges in JME often are maximally negative in the bifrontal regions. A lack of normal frontal lobe PET activation during visual working memory tests with JME patients suggests that the frontal cortex may not be functioning properly (1).

Frontal cortex has properties that could account for the generalized appearance of JME, including regional connectivity with the thalamus, widespread connections to ipsilateral and contralateral cortical regions, and motor cortex that could mediate myoclonus. The location and convoluted appearance of the frontal lobes make it difficult to identify subtle anatomic abnormalities. Similarly, impairment of frontal lobe executive functions, such as organization, planning, and complex social interactions, are often not noticed by patients and are difficult to detect by routine neurological examination. Thus, microscopic anatomic abnormalities or subtle defects of frontal lobe functions, if present in JME, could go unnoticed without careful quantitative assessment.

There is anatomical evidence of subtle frontal lobe abnormalities in JME. A few case series report focal cortical microdysgenesis in the frontal cortex; however, it is clear that this finding is only present in a small minority of cases (2). A more generally applicable observation is the increase in mesial frontal grey matter thickness seen in JME patients compared with controls, using quantitative MRI voxel-based morphometry (3). Similarly, MRS demonstrates reduced frontal lobe concentrations of *N*-acetyl aspartate in JME patients (4).

Evaluation of cognitive function for idiopathic generalized epilepsy is gaining attention because it provides evidence of focal brain dysfunction, which as mentioned, is counter to the traditional view that cognitive function is normal. Furthermore, it reveals the possibility that seizures arise from focal brain pathology in what appear otherwise to be truly generalized epilepsy syndromes. Some studies have reported psychiatric symptoms or cognitive deficits in patients with JME. There is greater impairment in frontal lobe test performance seen with JME patients compared with temporal lobe epilepsy patients as well as specific deficits in executive function for individuals with JME (5,6). A common problem in these studies is a lack of appropriate controls. Thus, it is possible that some deficits are due to antiepileptic drugs, the presence of seizure activity, or other phenomena generically related to epilepsy.

Piazzini et al., in the report reviewed here, performed a prospective assessment with JME patients using two commonly

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accepted neuropsychological tests of frontal lobe function: the Wisconsin Card Sorting Test and the Word Fluency Test. The investigators chose controls carefully to avoid problems present in previous studies; thus, patients with frontal lobe epilepsy were selected as a positive control group and a normal population without epilepsy also was used. A group with temporal lobe epilepsy was included to account for confounders common to all types of epilepsy, such as antiepileptic drug use and duration of epilepsy. The authors found a meaningful degree of cognitive deficit in the JME patients, who performed almost as poorly as the patients with frontal lobe epilepsy and much worse than the individuals with temporal lobe epilepsy.

The clinical implication of impaired frontal lobe function identified in the JME patients is not clear. The degree of deficit found by Piazzini et al. is significant for the group, but it is not obvious from the data presented what proportion of JME patients are affected. Are a few patients affected to a large degree or many patients affected to a moderate degree? As discussed, others have reported psychiatric problems in patients with JME, and frontal lobe dysfunction could contribute to this finding. It is important to recognize that at least some patients with JME may have psychosocial problems resulting from frontal lobe impairment.

How can the obvious clinical observation of JME as a generalized epilepsy be reconciled with the electrographic, imaging, and cognitive evidence of frontal lobe abnormalities? One hypothesis is that ongoing epileptiform activity alters frontal lobe physiology, resulting in altered neuropsychological function. This hypothesis seems unlikely since seizures are rare in JME and there is no simple reason why altered neuropsychological function would increase cortical thickness. A more likely hypothesis is that JME results from a fundamental abnormality of inhibitory neurotransmission that creates recurrent inhibition in circuits between the thalamus and susceptible neurons in the frontal cortex (7). Thus, the fundamental pathology could be in a multitude of locations, including thalamic neurons, frontal cortical neurons, or their connections—all of which result in the same phenotype. This theory could account for the variability of inheritance observed in JME, with some investigations suggesting JME is monogenic, while most cases are apparently polygenic. These hypotheses are speculative; however, overall the finding of focal frontal lobe dysfunction on neuropsychological testing in JME expands the possible explanations for its pathophysiology.

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Diagnosing Pseudoseizures: Don't Hold Your Breath

Postictal Breathing Pattern Distinguishes Epileptic from Nonepileptic Convulsive Seizures. Azar NJ, Tayah TF, Wang L, Song Y, Abou-Khalil BW. *Epilepsia* 2008;49(1):132–137. PURPOSE: To examine postictal breathing pattern in generalized convulsive nonepileptic seizures (GCNES) and generalized tonic–clonic seizures (GTCS) and evaluate this feature as a discriminating sign. METHODS: We reviewed the postictal breathing pattern seizures in 23 generalized tonic–clonic seizures in 15 consecutive patients with epilepsy and 24 convulsive nonepileptic seizures in 16 consecutive patients with pure psychogenic seizures. We also analyzed 21 frontal lobe hypermotor seizures (FLHS) in 9 patients with frontal lobe epilepsy. RESULTS: The breathing after GTCS was deep with prolonged inspiratory and expiratory phases, regular, and loud (except for two short seizures). The breathing after GCNES was characterized by increased respiratory rate or hyperpnea with short inspiratory and expiratory phases, as can be noted after exercise. The breathing was often irregular, with brief pauses. The altered breathing lasted longer after GTCS. The two groups differed significantly in loudness of postictal respiration, postictal snoring (only with GTCS), respiratory rate (faster for the GCNES group), and duration of altered breathing (longer after GTCS) ($p < 0.00001$ for all features). FLHS shared postictal breathing features of GCNES, but had other distinguishing features. CONCLUSIONS: The postictal breathing pattern can help differentiate generalized tonic–clonic seizures from nonepileptic psychogenic seizures with generalized motor activity and may be helpful to the practitioner obtaining a seizure history in the clinic setting or witnessing a seizure.

COMMENTARY

Discriminating between true seizures and pseudoseizures—even when they occur in front of a physician—long depended solely on behavioral clues. Yet just as a careful, step-by-step history of abnormal episodic symptoms or physical events always has been the cornerstone of epilepsy diagnosis, a meticulous history of potentially ambiguous episodes similarly can elicit reliable indicators of nonepileptic spells. Pelvic thrusting, bicycling leg movements, and violent thrashing were once confidently thought to be suggestive, if not diagnostic, of nonepileptic attacks. In contrast, incontinence, physical injury, and an initial positive response to a therapeutic trial of antiepileptic drugs generally were considered hallmarks of genuine seizures. The widespread use of 24-hour EEG video (EEG/video) monitoring, however, quickly undermined the validity of such clinical hallmarks (1). In particular, seizures arising from the frontal lobes proved to break most of the established assumptions. Hypermotor seizures (as they are termed by Azar et al. in this report) associated with frontal lobe epilepsy commonly display all of the behaviors thought to be virtually diagnostic of pseudoseizures, while EEG/video of pseudoseizures has revealed that urination, injury, and drug responsiveness may be part of many nonepileptic episodes (2,3). As a result, EEG/video has become the gold standard for discriminating between epileptic and nonepileptic attacks.

Because EEG/video is still not available to all clinicians, the neurological literature remains thick with studies, vignettes, and case histories aimed at suggesting or confirming the diagnosis of pseudoseizures on clinical grounds. Historical characteristics of pseudoseizures, including long duration, a start–stop pattern, directed actions, situational triggers (e.g., arguments, bizarre sensations or hallucinations, and weeping), have been identified by experienced clinicians and documented in case–control studies using EEG/video as being more common to pseudoseizures than to true seizures (4). However, clinical observations still may be important when an attack is observed first-hand by medical personnel. Identifying probable pseudoseizure symptoms or signs may be vital to a patient's welfare, as when someone presents to an emergency department with apparent status epilepticus (5). With an alert physician, historical features suggestive of pseudoseizures are used routinely as reasonable indications for more definitive diagnostic monitoring.

With few exceptions (e.g., shortness of breath associated with panic attacks), respiratory patterns are generally not a prominent part of a history of diagnostically puzzling spells. Although not well described in the medical literature, there are infrequent, anecdotal reports of focal seizures that begin with a sensation of catching one's breath or with an involuntary deep breath. The study by Azar et al. is one the first to focus on both ictal and postictal respiratory patterns of patients undergoing diagnostic EEG/video monitoring. The investigators demonstrate that respiratory patterns can be very sensitive and specific indicators of tonic–clonic or hypermotor seizures, on the one hand, and of convulsive-like but nonepileptic attacks, on the other hand. The study identifies certain other behavioral features, which reliably discriminate between epileptic and nonepileptic attacks or between tonic–clonic and hypermotor complex partial seizures. For instance, true tonic–clonic seizures—with their combination of postictal oxygen debt, accumulation of saliva, and reduced level of consciousness—are often followed by deep respirations and snoring or stertorous respiratory patterns. Such postictal respiratory patterns were

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found by Azar et al. to be highly specific for genuine tonic–clonic seizures (e.g., snoring in 61%), were never observed after pseudoseizures (0%), and occurred only rarely in hypermotor seizures (1 in 20). The diagnostic power of postictal stertorous breathing also was documented by Sen et al., who found that such respirations occurred in 41 of 44 confirmed tonic–clonic seizures and in none of 17 proven pseudoseizures (6). Another key diagnostic element identified by Azar and colleagues was the open or closed position of the patient's eyes during an episode: the eyes remained open in every tonic–clonic and hypermotor seizure but were closed in almost 90% of pseudoseizures, a finding documented in other studies as well (7).

Disappointing for diagnosticians in the report by Azar et al. was the lack of clinical features clearly separating pseudoseizures from hypermotor, usually frontal, seizures. Whereas deep breathing was seen postictally after every tonic–clonic seizure, shallow respirations characterized both pseudoseizures (13%) and hypermotor seizures (19%). The occurrence of pelvic thrusting ruled out a tonic–clonic seizure, but it was a nearly constant feature of both pseudoseizures and hypermotor seizures (>90%). Side-to-side head turning almost never occurred with tonic–clonic seizures (1 in 22) but was common in both hypermotor seizures (76%) and pseudoseizures (63%).

A meticulous history will remain important to discriminating between true epilepsy and nonepileptic attacks, and some of the findings of Azar et al. now can help clinicians to diagnose nonepileptic attacks more accurately. The noisy, deep breathing characteristic of the postictal phase of tonic–clonic seizures can be described vividly by most observers and used for diagnosis. In the emergency room, attention to postictal breathing patterns and ictal eye opening or closure may avoid unnecessary and sometimes risky therapy or conversely, spur clinicians to timely therapeutic action.

by Donna C. Bergen, MD

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Name Calling in the Temporal Lobe

Evidence for Cortical Reorganization of Language in Patients with Hippocampal Sclerosis. Hamberger MJ, Seidel WT, Goodman RR, Williams A, Perrine K, Devinsky O, McKhann GM 2nd. *Brain* 2007;130(Pt 11):2942–2950. Naming is mediated by perisylvian cortex in the left (language-dominant) hemisphere, and thus, left anterior temporal lobe resection for pharmacologically intractable temporal lobe epilepsy (TLE) carries risk for post-operative naming decline. Interestingly, this risk is lower in patients with hippocampal sclerosis (HS) relative to those without HS (non-HS). Although the hippocampus has traditionally been considered a critical structure for memory, without contribution to naming, this pattern might implicate direct hippocampal naming involvement. On the other hand, critical naming sites have been found in anterior, lateral temporal (i.e. extra-hippocampal) neocortex, the region typically removed with 'standard' TLE resection. We, therefore, speculated that the relative preservation of naming in post-operative HS patients might reflect cortical reorganization of language to areas outside this region. Using pre-resection electrical stimulation mapping, we compared the topography of auditory and visual naming sites in 12 patients with HS and 12 patients without structural brain pathology. Consistent with previous work, non-HS patients exhibited post-operative naming decline, whereas HS patients did not. As hypothesized, HS patients had proportionally fewer overall naming sites in anterior temporal cortex, the region typically removed with standard anterior temporal resection, whereas non-HS patients exhibited a more even distribution of naming sites in anterior and posterior temporal regions ($P = 0.03$). Although both groups exhibited the previously reported pattern of auditory naming sites anterior to visual naming sites, auditory naming sites had a significantly more posterior distribution in HS patients ($P = 0.02$). Additionally, non-HS patients exhibited a greater proportion of visual naming sites above the superior temporal sulcus, whereas visual naming sites in HS patients were scattered across superior and inferior temporal cortex. Results suggest that preserved naming ability in HS patients following anterior temporal resection might be attributable, at least in part, to intrahemispheric reorganization of language in response to the likely, early development of sclerosis in the medial temporal region. Furthermore, their more posterior distribution of naming sites is consistent with the more anterior propagation of EEG discharges in TLE. These results hold theoretical implications regarding the role of the dominant hippocampus in determining the cortical representation of semantic and lexical information, and raise questions regarding the specific roles of medial and lateral temporal cortex in targeted word retrieval. The different patterns of naming areas identified in patients with and without HS may also carry clinical implications, potentially improving efficiency during the time-constrained process of stimulation mapping.

COMMENTARY

In this study by Hamberger et al., auditory naming sites in the temporal lobe were found to reside anterior to visual naming sites, which reflect the anatomical locations of multisynaptic pathways that mediate their respective sensory processing. The ventral stream of visual processing involves successive engagement of Brodmann areas 17–21 en route to the lateral aspect of the temporal lobe (1). This pathway corresponds to areas of visual elaboration and ictal experiential phenomena that can be mapped by direct electrical stimulation of the human cortex (2). Auditory processing occurs in first- to third-order association areas of Brodmann area 22 of the superior temporal gyrus, after receiving input from primary auditory cortex (3). However, neurons in the anterior middle and inferior temporal gyri also participate in spoken speech, although these areas lay rostral to areas essential for speech integrity (3). Thus, any one of several verbal functions (i.e., naming, silent speech, reading, and short-term verbal memory) may activate neurons in the aforementioned areas (4). Although auditory and visual naming sites minimally overlapped in non-HS temporal lobe epilepsy patients in the present study, a previous study demonstrated that evoked potentials between the cortical sites in human disclosed pathways in each direction between anterior and posterior temporal and extratemporal language areas (5).

Several types of data indicate a close anatomical and functional connection between the hippocampus and temporal neocortex. First, anatomical studies have shown that hippocampal projections to the temporal neocortex are mediated through the subiculum and the entorhinal cortex; the anterior part of the superior temporal gyrus and the temporal polar cortex appear to be the principal lateral temporal recipients in primates (3,6). Second, extrahippocampal temporal lobe atrophy has been described in association with hippocampal sclerosis (HS) in patients with temporal lobe epilepsy (7). Third, PET studies in patients with mesial temporal epilepsy have revealed that temporal lobe hypometabolism extends over both its mesial and lateral aspects (8). Additionally, combined depth and subdural EEG recordings of hippocampal-originating seizures in humans found principal spread to temporal neocortex (9).

Some studies of verbal memory deficits after left temporal lobectomy correlate verbal memory loss with the extent of lateral temporal removal, while other studies correlate it with the amount of mesial temporal resection (3). Evidence is similarly mixed for naming. As in the current study, multiple prior

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reports have linked pathology and reduced function in the hippocampus to poor naming (10). Others have found postoperative naming changes associated with resection of larger volumes of neocortical tissue, regardless of whether or not surgery involved sparing of language eloquent cortex, as determined by stimulation mapping or anatomy (i.e., superior temporal gyrus) (11). Further, although strict damage to mesial structures from herpes simplex encephalitis often results in specific amnesia without deficits in naming or other measures of semantic memory, naming may be affected if lateral temporal cortex also is compromised (12).

The foregoing data suggest that naming and other verbal memory functions are the product of concerted mesial and lateral temporal activity. Hamberger et al. discuss further evidence of this hypothesis, which melds well with a more recent model of memory, called multiple trace theory, which emphasizes different strengths in the interactions and connections between these brain areas depending on whether the information was learned recently or more remotely. The multiple trace theory asserts that hippocampal regions may be involved in retrieving certain aspects of semantic memory (including object names), even if they are stored primarily in extrahippocampal cortex (13). This interactionist view helps interpret an interesting pattern reported in this and other studies (14), that is, the apparent greater sensitivity of the Boston Naming Test to postlobectomy changes compared with other visual naming measures. Hamberger et al. suggested that the greater proportion of low-frequency words in the Boston Naming Test might partly explain this finding. This theory is consistent with hypotheses in multiple trace theory and with the finding that words learned later in life are more susceptible to loss after anterior medial temporal lobectomy (15).

The current study found better post–temporal lobectomy naming among HS patients with as compared with non-HS patients, which correlated with a preoperative displacement of auditory naming posterior to usual dominant temporal lobe resections, as shown by preoperative or intraoperative mapping. No such displacement occurred among non-HS temporal lobe epilepsy patients. This finding is in alignment with the possibility that the persistent dysfunction associated with HS epilepsy will more effectively engender cortical reorganization than will intermittent disruptions associated with non-HS focal epilepsy. Furthermore, despite a greater total number of neocortical temporal naming areas in patients with HS, including anterior regions, naming was less affected by temporal resection. It has been suggested that cortical reorganization may produce a protective factor against postoperative decline, possibly because those additional language sites are redundant (11); however, cortical reorganization possibly may represent migration of functions normally mediated by nonsclerotic hippocampal tissue. Further investigation is necessary to better understand this apparent greater neuroplasticity.

Despite the lack of any study specifically linking post-temporal lobectomy naming ability with quality of life, the displacement of auditory naming sites to a more posterior distribution is good news for HS patients and their caregivers. The presence of HS is the most consistently demonstrated predictor of a good seizure outcome (16), substantially better than that for temporal lobectomy for which no lesion has been identified (17) and often predicts lower risk of postsurgical memory decline (18). Thus, HS may be the major factor linking the presence of three beneficial outcomes to left temporal lobectomy: 1) seizure freedom, 2) minimal change in verbal memory or naming, and 3) satisfactory quality of life (19,20). Results of the current study may underlie this favorable constellation.

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